A Non-Interventional Real-World Study on Dose Modifications of Enfortumab Vedotin (EV) in Combination with Pembrolizumab (P) in Previously Untreated Patients with Advanced Urothelial Carcinoma in Germany

EVERGREEN

ISN/Protocol 7465-MA-3558

Version 1.0

25-SEP-2024

Sponsor:

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SYNOPSIS

Title	EVERGREEN Study: A Non-Interventional Real-World Study on Dose Modifications of Enfortumab Vedotin (EV) in Combination with Pembrolizumab (P) in Previously Untreated Patients with Advanced Urothelial Carcinoma in Germany
Study identifier / Protocol Number	ISN: 7465-MA-3558
Protocol version & date of last version of protocol	Version: 1.0 Date: 25-SEP-2024
Active substance	Enfortumab Vedotin [ATC: L01FX13] + Pembrolizumab [ATC: L01FF02]
Medicinal product / Name of Assessed Drug(s)	PADCEV + KEYTRUDA
Product reference	EMA/44899/2022, EMA/515149/2023
Procedure number	Not applicable
Joint PASS	(Select one below) ☐ Yes ☒ No
Research question and objectives	The overall aim of this single arm, multi-center, non-interventional study, relying on primary data collection, is to provide real-world data on the administration of Enfortumab Vedotin and Pembrolizumab (EV+P) under routine conditions of daily clinical practice in Germany, in particular the management of dose modifications (dose reductions, interruptions, discontinuation). In addition, efficacy and safety of EV+P will also be collected.
Country of study	Germany
Number of Sites or Data Sources	25
Description of target population	A total of 150 patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing-chemotherapy, starting treatment with EV+P as first-line of therapy, aged 18 years or older at the time of treatment initiation and able to sign the informed consent form
Planned study period	Q1 2025 to Q4 2027
Author	PPD

MARKETING AUTHORIZATION HOLDER(S)

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Table of Contents

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2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviations	Description of Abbreviations
1L	First-Line of Therapy
AE	Adverse Event
CA	Competent Authorities
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
DCR	Disease Control Rate
ECOG-PF	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EV	Enfortumab Vedotin
EV+P	Enfortumab Vedotin and Pembrolizumab
HCP	Health Care Provider
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IME	Important Medical Event
IRB	Institutional Review Board
ISN	International Study Number
IV	Intravenous
MAH	Marketing Authorization Holders
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective Response Rate
OS	Overall Survival
P	Pembrolizumab
PD-1	Programmed Death Receptor 1
PD-L1	Programmed Death Receptor Ligand 1
PFS	Progression Free Survival
RA	Regulatory Authorities
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TTD	Time to Discontinuation
UC	Urothelial Carcinoma

Terms	Definition of Terms
Adverse Event	An adverse event is as any untoward medical occurrence in a patient administered a study drug and which does not necessarily have a causal relationship with this treatment.
Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a study by an enrolled patient.
Disease Control Rate	Proportion of patients who achieved partial response, complete response or stable disease to therapy
Investigational Period	Period of time where major interests of protocol objectives are observed, starting with the first evaluation or study visit and continuing until the last assessment or when the patient meets a withdrawal criterion.
Objective Response Rate	Proportion of patients who achieved a partial response or complete response to therapy
Overall Survival	Time (in months) from date of first dose of EV+P treatment to date of death due to any cause
Progression Free Survival	Time (in months) from date of the first dose of EV+P treatment to first documented clinical disease progression or death from any cause, whichever occurred first
Serious Adverse Event	An adverse event is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: results in death, is life-threatening, results in persistent or significant disability/ incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or a medically important event.
Study Period	Period of time from enrollment or initiation of data collection through to completion of study findings.
Subsequent Treatment	Initiation of systemic therapy after EV+P (index date)

3 AMENDMENTS AND UPDATES

Not applicable.

4 MILESTONES

The information provided in the Table is the initial planned dates and is not intended to be updated in the protocol if the planned dates change. Communication regarding shifts in the planned dates stated in the protocol will be done outside of an amendment to the protocol.

Milestone	**Planned Periods**
Ethic committee submission	Q4 2024
First patient in (FPI)	Q1 2025
Last patient in (LPI)	Q4 2025
Start of data collection	Q1 2025
End of data collection	Q4 2027
Final report of study results	Q1 2028

5 RATIONALE, BACKGROUND AND RESEARCH QUESTION

UC, especially advanced stage, is responsible for approximately 220,000 deaths worldwide annually [Bray et al, 2024]; the prognosis is poor with low 5-year survival rates (~5%) [Bharmal et al, 2017]. According to the latest report by the Robert Koch Institute, bladder cancer is the fourth most common cancer in men and the 13th most common in women in Germany [Robert-Koch-Institut, 2024].

EV is an antibody-drug conjugate targeting the molecule nectin-4 (highly expressed in UC) to deliver an antimitotic agent to the cancer cells. In April 2022, the EMA approved EV as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor [PADCEV SmPC, 2024]. In August 2017, the EMA approved P, a PD-1 inhibitor, as monotherapy for the treatment of unresectable or metastatic urothelial cancer in adults who have received prior platinum-containing chemotherapy, or who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score equal to or higher than 10 [KEYTRUDA SmPC, 2024].

Recently, the combination of EV+P has demonstrated a survival benefit compared to chemotherapy (OS of median 31.5 *versus* 16.1 months, with hazard ratio of 0.47 (0.38-0.58)) in previously untreated unresectable or metastatic urothelial cancer patients in the pivotal phase 3 study EV-302/KEYNOTE-A39 [Powles et al, 2024]. Considering the positive survival results, in August 2024, the EMA approved the combination of EV+P for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [European Medicines Agency, 2024].

Based on clinical studies, it is known that dose modifications have a key role in the AE management of EV [Powles et al, 2021; Powles et al, 2024]. In EV-302, treatment-related AE led to the discontinuation of EV in 29.5% of the patients and treatment-related AEs resulting in dose reduction of any treatment occurred in 40.7% of the patients in the EV+P group (440 patients). In 60.5% of the patients, EV was interrupted due to treatment-related AE [Powles et al, 2024]. However, these findings offer a limited insight into the real-world handling of dosage in 1L unresectable or metastatic urothelial cancer patients with EV+P in routine clinical practice. As EV+P is a new combination with some overlapping toxicity profile, the real-world handling of these drugs in combination, especially dose modification, is of high clinical relevance to ensure effective AE management and tumor control.

The overall aim of this single arm, multi-center, non-interventional study, relying on primary data collection, is to provide real-world evidence on the administration of EV+P under routine conditions of daily clinical practice in Germany, in particular the management of dose modifications (dose reductions, interruptions, discontinuation). In addition, efficacy and safety data will be collected.

6 OBJECTIVES, ENDPOINTS AND ESTIMANDS

6.1 Study Objectives and Endpoints

Table 1. Study objectives and endpoints

Objectives	Endpoints
Primary	
● To describe the frequency of real-world dose modifications in 1L unresectable or metastatic urothelial cancer patients receiving EV+P	● Dose modification (dose reduction, temporary interruption, permanent discontinuation) for EV and/or P
Secondary	
● To describe the frequency of real-world specific types of dose modifications of EV+P and reasons for specific dose modifications	● Permanent discontinuation of EV and/or P ● Temporary interruption of EV and/or P ● Dose reduction of EV ● Dose received following temporary interruption ● Reason for permanent discontinuation of EV and/or P ● Reason for temporary interruption of EV and/or P ● Reason for dose reduction of EV ● Overall duration of treatment with EV, P and EV+P
● To describe real-world effectiveness of EV+P based on PFS	● Disease progression (defined as clinical progression or death)
● To describe real-world effectiveness of EV+P based on OS	● OS (defined as the time from date of first dose of EV+P treatment to date of death due to any cause)
● To evaluate real-world effectiveness of EV+P based on tumor response (ORR)	● ORR (defined as the proportion of patients who achieved a partial or complete response to therapy)
● To evaluate disease control rate of EV+P	● Disease control rate (defined as the proportion of patients who achieved stable disease, partial response, or complete response)
● To describe clinical safety, related to the use of EV+P in the real-world	● All TEAE Grade ≥ 3 for EV and/or P ● All TEAE that led to dose modifications ● Frequency of observed improvement/resolution of all TEAE† Grade ≥ 3 or all TEAE that led to dose modifications of EV and/or P.

1L: first-line of therapy; AE: adverse event; EV: Enfortumab Vedotin; EV+P: Enfortumab Vedotin and Pembrolizumab; ORR: objective response rate; OS, overall survival; P: Pembrolizumab; PFS: progression free survival; TEAE: treatment-emergent adverse event

[†]TEAE and dose modifications will be collected over the duration of the therapy with EV+P, until both treatments are permanently discontinued. Causation of TEAE with EV or P will not be documented.

6.2 Estimands

The estimand for the primary objective is defined by the following 4 attributes:

Population: unresectable or metastatic urothelial cancer patients initiating EV+P as 1L in Germany.

Endpoint: A composite dose modification endpoint consisting of dose reduction, temporary interruption, and permanent discontinuation.

Intercurrent events for the primary objective and their corresponding strategies:

Intercurrent events	Strategies to handle intercurrent events
Loss to follow-up	Censor patient at date of last visit
Death	Competing event
Permanent discontinuation of EV	Event of discontinuation that also comprises “dose modification” composite endpoint. Follow-up continues until P is discontinued or follow-up ends.
Permanent discontinuation of P	Event of discontinuation that also comprises “dose modification” composite endpoint. Follow-up continues until EV is discontinued or follow-up ends.
2 years of follow-up after first dose of EV+P	Censor
Progression	Ignore

EV: Enfortumab Vedotin; EV+P: Enfortumab Vedotin and Pembrolizumab; P: Pembrolizumab

Population level summary: Cumulative incidence of dose modification for unresectable or metastatic urothelial cancer patients initiating EV+P in 1L in Germany.

7 RESEARCH METHODS

7.1 Study Design

This is a single arm, multi-center, non-interventional prospective cohort study which aims to describe the use of EV+P, especially, the dose modification, in previously untreated patients with unresectable or metastatic urothelial cancer in Germany. Data will be collected prospectively in approximately 25 sites in Germany.
Patients who meet all the eligibility criteria, including initiating EV+P for the first time (as described in sections 7.2.1 and 7.2.2) will be considered. The index date will correspond to the date of the first administration of EV+P treatment after informed consent signature. At index date, information on patients’ demographic and clinical characteristics (as described in sections 7.3) prior to starting EV+P will be collected. In addition, data will be collected at the time of dose modifications, including reason for dose modifications, safety-related information, real-world efficacy assessments, and at end of follow-up, namely patient disposition.

For dose modification:

- Data will be collected until treatment discontinuation of EV and P, until start of subsequent treatment, end of study period (2-years after first dose of EV+P treatment), death or withdrawal of consent, whichever occurs first.

For ORR, DCR, PFS:

- Data will be collected until start of subsequent treatment, end of study period (2-years after first dose of EV+P treatment), death, or withdrawal of consent, whichever occurs first.

For TEAEs other than death

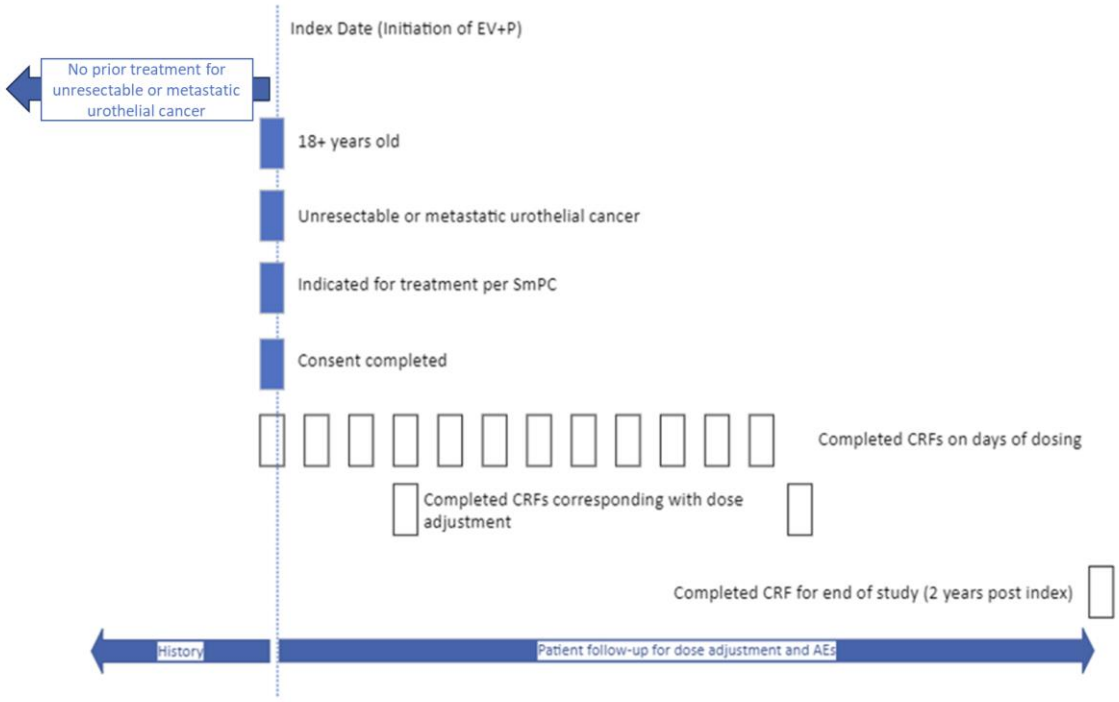
- Data will be collected until treatment discontinuation of EV and P + 90 days, end of study period (2-years of EV+P treatment), death, or withdrawal of consent, whichever occurs first.

For OS:

- Data will be collected until end of study period (2-years after first dose of EV+P), death, or withdrawal of consent, whichever occurs first.

Due to the observational nature of this study, study visits, types of performed treatments and assessments will occur according to routine clinical practice. Figure 1 illustrates the study design and the follow-up.

Figure 1. Study design



AE: adverse event; CRF: case report form; EV+P: Enfortumab Vedotin and Pembrolizumab; SmPC: summary of product characteristics

7.1.1 Data Sources

Patients will be recruited prospectively from approximately 25 sites, both office based and hospital uro-oncologists and medical oncologists across Germany. To allow for a reasonable geographic spread and representation of different institution types to support representative sample of real-world treatment setting in Germany, a feasibility assessment of sites is performed. Out of this assessment, sites that meet the criteria described above will be selected.

The study will be based on collection of primary data by observation and documentation. Study physicians will document the information over a period of 2 years per patient.

No additional visits, assessments or procedures are required in this study.

All required data will be entered into a study specific eCRF under the supervision of the study physician.

7.2 Study Population

A total of 150 patients aged 18 years and older will be enrolled across approximately 25 sites in Germany. Patients starting treatment between Q1 2025 and Q3 2025 who meet study eligibility criteria will be considered for the study.

Patient exclusion criteria will be determined according to SmPC [KEYTRUDA SmPC, 2024; PADCEV SmPC, 2024].

Approximately 25 sites are selected to allow a reasonable geographic spread and representation of different institution types to support representative sample of real-world treatment setting in Germany. To ensure representativeness, a temporary capping is applied to all sites for 3 months depending on the potential recruitment rates. After 3 months the cap will be lifted for full competitive recruitment.

7.2.1 Inclusion Criteria

1. 1L unresectable or metastatic urothelial cancer patient starting treatment with EV+P (decision for treatment made by treating physician according to local clinical practice independent of and prior to enrollment in study and based on SmPC).
2. Patient is 18 years of age or older at the time they start EV+P.
3. Consent of the patient.

7.2.2 Exclusion Criteria

1. Exclusion and eligibility criteria will be determined according to the SmPC.
2. Patient with ongoing or planned participation in interventional clinical trials evaluating the combination of EV+P.

7.2.3 Discontinuation Criteria

A patient is free to withdraw from the study for any reason, at any time, without reason for doing so and without penalty or prejudice.

At the end of a patient involvement in this study, the Investigator must ensure that all outstanding data entry is entered in the eCRF unless the patient withdrew consent for his or her data to be used.

7.3 Treatments and Evaluation

7.3.1 Enfortumab Vedotin and Pembrolizumab Treatment

According to the SmPC, EV is administered at a dose of 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) on day 1 and day 8 of every 3-week cycle by IV infusion given over approximately 30 minutes [PADCEV SmPC, 2024], and P is administered at a dose of 200 mg on day 1 of every 3-week cycle or 400 mg every 6 weeks by IV infusion given over approximately 30 minutes after completion of EV [KEYTRUDA SmPC, 2024]. According to the SmPC, dose reductions, temporary interruptions and permanent discontinuations are recommended approaches to manage AE for EV [PADCEV SmPC, 2024], and no dose reduction is recommended for P, but it should be withheld or permanently discontinued in the case of adverse reactions [KEYTRUDA SmPC, 2024].

7.3.2 Baseline Assessments

At the index date (i.e., date of first administration of EV+P), the following information will be collected: clinical and demographic characteristics including age, sex, ECOG-PS, primary site of tumor, dimension of tumor or lesion, tumor stage at diagnosis and at EV+P treatment initiation (locally advanced *versus* metastatic), metastatic site(s) at diagnosis and at EV+P treatment initiation, treatment center type and location (department level), renal function (i.e., creatinine clearance [mL/min]), history of peripheral neuropathy, history of hyperglycemia, prior neoadjuvant or adjuvant treatment of UC, weight, and height.

7.3.3 Post Baseline Assessments

During the follow-up, the following data will be collected: EV+P treatment information such as administered dosage, date of administration, number of dose reductions of EV, date and reasons for dose reductions of EV, number of temporary interruptions of EV and/or P, start and end date and reasons for temporary interruptions of EV and/or P, administered dosage following temporary interruption, and date and reasons for permanent discontinuation (i.e., withdrawal, lost to follow-up, death, tumor progression, AE).

In each routine visit, the study physician advises if patient requires any dose modification in their treatment as per the patient’s needs. In case tumor response/progression is assessed according to clinical practice, this will be documented for the corresponding visit. Tumor response includes complete response, partial response, or stable disease, as per clinical judgment. Data on tumor response will be collected upon availability.

All TEAE that led to dose modification or were grade 3 or higher, will be recorded by the study physician (for all AE definitions, see Section 12, Annex 4).

7.4 Schedule of Assessments

Table 2. Schedule of Assessments

Assessments/Procedure	Responsible party	Index (Baseline)	Study treatment period (2 years) Visit(s) during dose modification/ follow-up	Unscheduled according to clinical practice	End of treatment of EV and P
			Each dose of EV and/or P given		
Informed consent, inclusion and exclusion criteria	Recruiting physician	X			
Demographics and clinical characteristics • Age • Sex • ECOG-PS • Primary site of tumor • Dimension of the tumor • Tumor stage at diagnosis and at start of EV+P treatment (locally advanced *versus* metastatic) • Metastatic site(s) at diagnosis and start of EV+P treatment • Treatment center type and location (department level) • Renal function (creatinine clearance)	Recruiting physician	X			
Medical history • History of peripheral neuropathy • History of hyperglycemia • History of skin conditions • Prior treatments for UC	Recruiting physician	X			

(adjuvant/neoadjuvant/ radical cystectomy/radical nephroureterectomy/EV monotherapy/P monotherapy)					
Weight and height	Recruiting physician	X			
Post baseline tumor assessment • Tumor response • Tumor progression	Recruiting physician			X	
Study drug exposure – Infusion (modifications, interruptions, discontinuation)† • Administered dosage • Date of administration • Number, date and reason(s) for dose reductions of EV • Number, start, end date and reason(s) for temporary interruptions of EV and/or P • Administered dosage following temporary interruption • Date and reason(s) for permanent discontinuation (withdrawal, lost to follow-up, death, tumor progression, AE)	Recruiting physician		X		
Subsequent treatment after EV+P				X	
Safety • All TEAE that led to dose modifications • All TEAE Grade ≥ 3 for EV and/or P • Improvement/resolution of all TEAE‡ Grade≥3 for EV and/or P or all TEAE‡ that led to dose modifications of EV and/or P	Recruiting physician			X	

Death	Recruiting physician			X (as occurred)	
End of treatment Reason • Lost to follow-up • Withdrawn consent	Recruiting physician			X (as occurred)	

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; EV: Enfortumab Vedotin; EV+P: Enfortumab Vedotin and Pembrolizumab; P: Pembrolizumab; UC: urothelial carcinoma

†Dose modifications are documented for each dose of EV administered. Per SmPC EV will be administered on day 1 and day 8, and P will be administered on day 1 of each 21-day cycle. Skipped doses/treatment interruption and discontinuation are documented using a query.

‡TEAE and dose modifications will be collected over the duration of the therapy with EV+P, until both treatments are permanently discontinued. Causation of TEAE with EV or P will not be documented.

7.5 Study Size

A total of 150 patients with unresectable or metastatic urothelial cancer aged 18 years and older will be enrolled across approximately 25 sites in Germany. This number will yield an appropriate precision to assess the frequency of real-world dose modifications in unresectable or metastatic urothelial cancer patients receiving EV+P as 1L. A precision statement is provided in section 7.7.1.

7.6 Data Management

Data management will be in accordance with the SOP of the CRO. All study specific processes and definitions will be documented by IQVIA.

All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual site and its own enrolled patients. All sites will be fully trained in using the online data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRF should be completed by designated, trained personnel or the study coordinator, as appropriate. At the end of data collection, the eCRF will be reviewed and electronically signed by the principal investigator. All changes or corrections to eCRF will be documented in an audit trail and an adequate explanation is required.

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRF will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed. Ad hoc queries will be generated within the EDC system and followed-up for resolution.

High data quality standards will be maintained and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for

analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

Coding of medical terms and medications will be performed MedDRA and World Health Organization Drug Dictionary respectively.

7.7 Statistical Methods

7.7.1 Sample Size Justification

The study aims to enroll 150 patients from approximately 25 sites in Germany. It is expected that around 50% to 60% of patients will require a dose modification. Sample size justification is based on precision.

When the sample size is 150, a two-sided 95% CI for a single proportion using the large sample normal approximation will extend 0.080 from the observed proportion for an expected proportion of 0.5 (bolded cells).

Table 3. Study sample size

		99% CI		95% CI		90% CI	
n = 150	Probability of event	Lower	Upper	Lower	Upper	Lower	Upper
	0.30	0.204	0.396	0.227	0.373	0.238	0.362
	0.40	0.297	0.503	0.322	0.478	0.333	0.467
	0.50	0.395	0.605	**0.420**	**0.580**	0.433	0.567
	0.60	0.497	0.703	0.522	0.678	0.533	0.667
	0.70	0.604	0.796	0.627	0.773	0.638	0.762

Lower CI = P – W, Upper CI = P + W

W = z * sqrt (pq/n)

Abbreviations: CI, confidence interval; P, proportion; q, 1-proportion; sqrt, square root; W, width; z, z statistic

7.7.2 Statistical Analysis

Data analysis will be performed by the CRO in accordance with the CRO's SOP for statistics and clinical programming with oversight from the Data Science Department of Astellas. All study specific processes and definitions will be documented, including the creation of a Statistical Analysis Plan that further details the analysis. Data analysis will be performed in adherence to Astellas standards.

Descriptive analyses for continuous variables include means, medians, and standard deviations, while categorical variables will be summarized using counts and percentages.

The study includes a large number of endpoints. The period of observation used for the analysis varies across endpoints. The Table 4 below provides an overview of how intercurrent events are handled for each endpoint.

Table 4. Handling of intercurrent events for each endpoint

Endpoint/ Intercurrent event	**2 years after first dose of EV+P**	**Death**	**Progression**	**Lost to follow-up**	**Interruption/ Dose reduction**	**Treatment Discontinuation of EV and P**	**Subsequent treatment start**
Dose modification	Censor	Competing event	Ignore	Censor	Case	Case	Ignore
Permanent discontinuation	Censor	Competing event	Ignore	Censor	Ignore	Case	Ignore
Temporary interruption	Censor	Competing event	Ignore	Censor	Case	Competing event	Ignore
Dose reduction	Censor	Competing event	Ignore	Censor	Case	Competing event	Ignore
OS	Censor	Case	Ignore	Censor	Ignore	Ignore	Ignore
PFS	Censor	Case	Case	Censor	Ignore	Ignore	Censor
ORR	Censor	Competing event	Competing event	Censor	Ignore	Ignore	Censor
DCR	Censor	Competing event	Competing event	Censor	Ignore	Ignore	Censor
TTD	Censor	Case	Ignore	Censor	Ignore	Case	Ignore
Endpoint/Intercurrent event	2 years after first dose of EV+P	Death	Progression	Lost to follow-up	Interruption/ Dose reduction	Treatment Discontinuation of EV and P	Subsequent treatment start
TEAE, other than death	Censor	Competing Event	Ignore	Censor	Ignore	Censor 90 days following treatment discontinuation	Censor

AE: adverse event; DCR: disease control rate; EV: Enfortumab Vedotin; EV+P: Enfortumab Vedotin and Pembrolizumab; ORR: overall response rate; OS: overall survival; P: Pembrolizumab; PFS: progression free survival; TEAE: treatment-emergent adverse event; TTD: time to treatment discontinuation

1. Analysis of Patients at Index Date

Patient characteristics including demographics and medical history collected at index date will be analyzed descriptively.

2. Analysis of Primary Objective

In order to describe the frequency of real-world dose modifications in 1L unresectable or metastatic urothelial cancer patients receiving EV+P, dose modification of EV and/or P will be analyzed as a composite variable of dose reduction, temporary dose interruption, and permanent discontinuation. The frequency of patients experiencing dose modification will be descriptively analyzed. Cumulative incidence of dose modification will be estimated using survival analysis; death will be considered a competing event.

3. Analyses of Secondary Objectives

a. Dose Modification

The frequency of patients experiencing the endpoint (i.e., dose reductions, temporary treatment interruption, and permanent treatment discontinuation) will be descriptively analyzed. The frequency of specific types of real-world dose modifications for EV and/or P in EV+P patients (i.e., dose reductions, temporary treatment interruption, and permanent treatment discontinuation) will be described.

Cumulative incidence of dose modification will be estimated using survival analysis. Death will be considered a competing event. For permanent discontinuation and treatment temporary interruptions, the cumulative incidence will be estimated for EV (e.g., time to date of permanent discontinuation of EV), P (e.g., time to date of permanent discontinuation of P), and EV+P (e.g., time to date of permanent discontinuation of EV and P).

Among patients experiencing a dose modification, the frequency of reasons for dose modification will be described by type of dose modification.

Among patients experiencing a temporary treatment interruption, dose modification will be described following temporary interruption (e.g., same dose *versus* dose reduction) for EV and P.

b. OS and PFS

OS and PFS will be estimated using Kaplan-Meier approach. Probability of survival will be reported for 12- and 24-months post-index. An interim analysis of OS will be conducted 12 months after enrollment is completed. Depending on the rate of events during the course of follow-up, median OS/PFS will not be reported if median OS/PFS is not reached.

c. ORR and DCR

Upon availability, ORR and DCR will be analyzed descriptively by dose modification categories (i.e., dose modification, treatment interruption and treatment discontinuation). Cumulative incidence of ORR and DCR will be estimated using survival analysis, and death

will be considered a competing event. The frequency distribution of best overall response data will be described.

d. AE

The frequency of TEAEs will be analyzed descriptively by grade and time to onset. Among patients experiencing AEs leading to dose modification or AEs Grade 3 or greater, the frequency of AE improvement/resolution will be reported upon availability.

7.7.3 Planned Analyses

1. Baseline analysis: Start at data freeze Q3 2025 (after last patient entered the study); report completed Q4 2025
2. Interim analysis: Q3 2026 (data freeze 1 year after last patient entered the study)
3. Final analysis: Q4 2027 (2 years after last patient entered the study)

7.8 Quality Control

7.8.1 Non-Interventional Study Monitoring

Sites will be managed and monitored throughout the duration of the study and according to the approved Site Management and Monitoring Plan. Trained and qualified personnel of the CRO will oversee site participation by means of a combination of remote site management (e.g., via telephone calls) and on-site monitoring visits, with partial source data verification. The on-site visits will be conducted to assess the data quality and study integrity.

In addition, the study may be evaluated by the sponsor's internal auditors and government inspectors who must be allowed access to eCRF, source documents, other study files, and study facilities. Astellas' audit reports will be kept confidential.

The study physician must notify Astellas promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Astellas.

7.8.2 Direct Access to Source Documents

The Investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the relevant regulatory authorities. In these instances, the Investigator must provide all study-related records such as source documents when they are requested by the monitors, auditors, or regulatory authorities. The confidentiality of the patients shall be protected, consistent with local and national regulations.

7.9 Limitations of the Research Methods

A potential limitation of this study might be a selection bias due to inclusion of patients with a treatment combination which has recently been approved. However, efforts will be made to include a diverse study cohort to reflect the real-world setting.

Another limitation might be an attrition bias emerging from lost to follow-up, as in any longitudinal study. However, the lost to follow-up is considered as an intercurrent event and will be handled by censoring the patients at date of last visit in survival analysis.

Furthermore, information bias might occur due to missing data on medical records.

Considering the descriptive nature of this study, no inference on causality can be done.

8 PROTECTION OF PATIENTS

This study will be conducted in compliance with all applicable requirements in Germany for ensuring the rights of patients in non-interventional studies.

8.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA) / Regulatory Authorities (RA)

Where any IRB/ IEC/ CA/ RA approval is required, the study can only begin after acquisition of a written approval/favorable opinion from such Board/Committee/Authority. The approval/favorable opinion must contain:

- Identity of the study
- Date of review
- Documents reviewed (if available)
- List of names, titles, and professions of the members of the committee in the case of IRB/IEC favorable opinion (if available)

The original or copy of the approval/favorable opinion should be submitted to the sponsor or sponsor's designee.

In the name of the Investigator the CRO will submit accurate and adequate reports to the applicable IRB/IEC/CA/RA within the timelines as per local and national requirements.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki.

8.3 Patient Information and Consent

- The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.
- The information provided shall be provided in writing and shall:
  - enable the patient to understand:
    - the nature, objectives, benefits, and inconveniences of the study
    - the conditions under which the study is to be conducted, including the expected duration of the patient's involvement in the study
  - be kept comprehensive, concise, clear, relevant, and understandable to a layperson.
  - be provided in a prior interview with an appropriately qualified member of the study team. Special attention shall be paid to the information needs of specific patient

populations and of individual patients, as well as to the methods used to give the information. Care should be taken to verify that the patient has understood the information.
    - include information about the applicable damage compensation system, in the regions where it is required.
    - include the study ISN and information about the future availability of the study results in terms understandable to a layperson.
    - include information about why, how and for how long patient's personal information will be processed; with whom his/her personal information may be shared and if it transferred beyond the country of origin; how patients can exercise their data protection rights and how they can contact the sponsor and the sponsor's data protection office.
    - include any other information that may be required according to the applicable local laws and regulations.
- Patients must be informed that their participation is voluntary and shall have their protective rights and guarantees explained, including their privacy rights. In particular, their right to refuse to participate and the right to withdraw from the study at any time without any resulting detriment and without having to provide any justification shall be explained.
- Patients will be required to sign a statement of informed consent that meets the requirements of the IRB/IEC or study center and includes consent about the processing of personal information. The informed consent shall be kept in the medical record of patients. The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients may be required to reconsent to the most current version of the ICF during their participation in the study, if there are material changes in the study.
- A copy of the ICF must be provided to the patient.

8.4 Patient Confidentiality

Astellas maintains confidentiality standards by ensuring that it does not receive from Investigators names or other directly identifying personal information of patients in any CRF or other documents submitted to the sponsor (unless this is required by law for reporting of AE). In particular, a patient identification number will be used at inclusion to serve as the patient's identifiers in the study, as well in the study database retained by the sponsor. Documents not for submission to the sponsor, such as signed ICF (where required and applicable), are maintained in strict confidence by the Investigator in the medical file of the patient at site.

The sponsor will use the personal information collected from patients to run the study and to use and publish the results of the study.

Individual patient medical information obtained as a result of this study is considered strictly confidential and disclosure to third parties is allowed only according to this protocol and any

ICF signed (if applicable). Such medical information may be given to the patient's physician or to other appropriate medical personnel responsible for the patient's well-being.

Data generated by this study, including personal information of the patients and their medical information, must be available for inspection by the sponsor, the sponsor's authorized representative(s), the IRB/IEC and, when necessary, representatives of the relevant regulatory health authorities. Only authorized persons will have access to identifiable personal information, if required.

All study reports will contain aggregate data only and will not identify any individual patients.

The sponsor will inform the patients about their privacy rights and how to exercise them under the ICF which patients will sign in order to participate in the study.

Patients will be entitled to contact Astellas Group Data Protection Officer at privacy@astellas.com with questions about the use and protection of their personal information when they participate in a study.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing patient's personal information.

8.5 Insurance of Patients

Not applicable.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

Reporting to Astellas Pharmacovigilance is required for all AE in which any Astellas drug has been administered, regardless of the purpose of the study. Reporting to Astellas Pharmacovigilance is not required for non-Astellas drugs unless the drug is a co-suspect drug for an Astellas drug AE or if it is related to the study objective (i.e., a study drug). Investigators are required to forward these non-Astellas drug AE to the MAH.

9.1 Primary Data Collection

Information on all AE associated with the use of Astellas products should be collected and reported to Astellas Pharmacovigilance per the timelines and e-mail addresses described in Section 9.5. A causality assessment from the primary source should be obtained as described in Section 9.3. If this is not available, enough information should be collected to allow the sponsor to perform the causality assessment.

Events related to non-Astellas drugs are not required to be reported to Astellas Pharmacovigilance; however, it is the investigator's responsibility to forward these events to the relevant MAH.

9.2 Secondary Data Collection

Not applicable.

9.3 Criteria for Causal Relationship to the (Study) Drug

A medically qualified investigator is obligated to assess the relationship between EV, P and EV+P combination, and each occurrence of each AE/ SAE using clinical judgment to determine the relationship along with the local label. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may revise his/her assessment of causality in light of new information regarding the AE/SAE and shall send an AE/SAE follow-up report and update the eCRF with the new information and updated causality assessment.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an AE/SAE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and AE/SAE onset and/or resolution. Has the patient actually received the study drug? Did the AE/SAE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility: i.e., could the event have been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.,
- Dechallenge/Dose reduction/Rechallenge:
  - Did the AE/SAE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
  - Did the AE/SAE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the AE/SAE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation

There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the medically qualified investigator always makes an assessment of causality for every event before the initial transmission of the AE/SAE data to the sponsor. With limited or insufficient information about the event to make an informed judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the AE/SAE as soon as possible and to re-evaluate the causality upon receipt of additional information.

9.4 Procedure in Case of Pregnancy

Reporting Pregnancy

If a female patient or partner of a male patient becomes pregnant during the study while taking the medication the investigator is to report the information to the sponsor as if it is an SAE according to timelines in Section 9.5 using the Pregnancy Reporting Form. When pregnancy is confirmed, the patient must be followed-up until completion of the pregnancy. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and outcome/neonatal data etc., should be included in this information. If limited data are reported, reasonable effort should be made to collect complete information. Follow instructions per product label regarding pregnancy.

The pregnancy itself is not considered to be an AE/SAE but, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported as an SAE.

When the outcome of the pregnancy falls under the criteria for SAE [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAE. Additional information regarding a pregnancy outcome that has been categorized as an SAE is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within one month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than one month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator

Partner Pregnancy of a Male Patient

If during the conduct of a clinical study, a male patient makes his partner pregnant, the patient should report the pregnancy, including the paternal exposure, to the investigator. The investigator will report the pregnancy to the sponsor as an SAE.

9.5 Notification of Adverse Events (Serious and Non-serious) by Study Personnel to Sponsor

For a Serious/Fatal AE, the investigator must complete and submit an Astellas Safety Information Report Form [or equivalent] containing all information that is required by the RA to the sponsor by fax or e-mail immediately (within 24 hours of awareness). If the faxing or e-mailing of an ICSR AE and Special Situation Form is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

In the case of a non-serious AE, the investigator must contact sponsor by fax or e-mail immediately (within 72 hours of awareness).

When submitting an Astellas Safety Information Report Form [or equivalent], the following information is required:

- ISN/Study number
- Patient number, sex, and age
- The date of report
- A description of the event including seriousness criteria
- Causal relationship to the study drug (including reason)
- The drug provided

The Astellas Safety Information Report Form [or equivalent] must be signed by a medically qualified Investigator or Sub-Investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data as well as the Investigator causality assessment.

In the case of all other new non-serious AE, the investigator also must contact the sponsor by fax or e-mail immediately (within 72 hours of awareness) using the Astellas Safety Information Report Form (or equivalent). Reporting is to begin following receipt of the informed consent (if required) and will continue to the end of the patient's participation in the study. All new AE collected for the study will be recorded, organized and summarized for inclusion in the final study report after coding as per MedDRA dictionary.

Guidance for Reporting AE/Special Situations to PV:

Reporting to Pharmacovigilance (Section 12, Annex 4)	**Timelines**
Serious/Fatal Adverse Events	Within 24 hours of awareness
Non-serious AEs	Within 72 hours of awareness
Special Situations	Within 72 hours of awareness
Pregnancy	Within 72 hours of awareness

For reporting to Global Pharmacovigilance – EU:
Europe :
Fax : +31 71 545 5208
E-mail : Safety-EU@astellas.com

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A study report will be prepared summarizing the study design, analysis and final results of the study. Upon study completion and study report finalization, the results of this observational study will be considered for dissemination in the form of peer reviewed publications and/or presentations at scientific conferences.

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12 ANNEXES

Annex 1 List of Stand-Alone Documents

Not applicable.

Annex 2 Non-Interventional Study Continuity

Not applicable.

Annex 3 ENCePP checklist for study protocols

Not applicable.

Annex 4 Definitions

DEFINITION OF ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a patient administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal (investigational) product.

In order to identify any events that may be associated with study assessments and could lead to a change in the conduct of the study, Astellas collects AEs even if the patient has not received study drug treatment.

Use the following criteria to determine if an abnormality identified during a medical assessment should be identified as an AE:

- Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., electrocardiograms, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an AE/SAE.
- Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an AE/SAE, unless judged by the investigator to be more severe than expected for the patient's condition.
- Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it:

- Results in death.
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect of a child conceived during the exposure of one of the parents to the drug studied.
- Requires inpatient hospitalization or leads to prolongation of hospitalization. (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IME that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The sponsor has a list of events that they classify as "IME". If an AE is reported that is considered to be an "IME", additional information on the event may be requested by the sponsor.

DEFINITION OF SPECIAL SITUATIONS

The following Special Situations are not considered AEs, but they do require collection and communication to Astellas as per timelines described in the Table above: **Guidance for Reporting AE/Special Situations to PV**.

Special Situations are:

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Drug exposure during pregnancy and/or breast-feeding.
- Lack of efficacy/effectiveness.
    - Some countries may have additional local requirements for events that are required to be reported as AE or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AE or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly. For example, unusual failure in efficacy is required to be reported as an AE in Canada when the study involves a marketed product.
- A review of local requirements for additional reporting requirements must be done before initiating the study to ensure appropriate communication on the additional requirements for reporting.
- Medication error refers to an inadvertent, unintentional, or unsupervised action by either HCP, patient, or consumer. This may involve the drug treatment process including the prescription, dispensing, storage or administration of a medicinal product or dosage regimen that is not consistent with that intended in the authorized Product Information

Medication Errors are collected even when they are not associated with any AE/SAE. Medication errors can include the following:

- Intercepted medication error: an intervention caused a break in the chain of events in the treatment process before reaching the patient, which would have resulted in a 'potential' harm/AE.
- Potential medication error: the recognition of circumstances that could realistically lead to a medication error while the medication is in the control of an HCP, patient, or consumer, and may or may not involve a patient.

- Occupational exposure: this refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation.
- Suspected drug-drug interaction.
- (Suspicion of) transmission of infectious agent.

All Special Situations noted above should be recorded on the (e)CRF. Any situation that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and Astellas form (STL-3303 ICSR Adverse Event and Special Situation Form).

All Special Situations noted above should be recorded on the (e)CRF. Any situation that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and Astellas form (STL-4520 Astellas Safety Information Report Form)

SIGNATURES

COORDINATING INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree that it contains all the information required to conduct this study.

Coordinating Investigator:

Signature: _____ .....
<Insert name, department/affiliation, name of institution> Date (DD Mmm YYYY)

Printed Name**:** _____ .....

Address: _____ .....

_____ .....

INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I will also ensure that any sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and applicable non-interventional guidelines (European Medicines Agency, Guideline on good pharmacovigilance practices) to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ....
<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: ....

Address: ....

....

Protocol Approval Committee

Signature:

PPD

Date (DD Mmm YYYY)

Global Oncology PPD

Signature:

PPD

Date (DD Mmm YYYY)

MA-EST-M

Signature:

PPD

Date (DD Mmm YYYY)

MA-France

Signature:

PPD

Date (DD Mmm YYYY)

Oncology

Signature:

PPD

Date (DD Mmm YYYY)

Oncology

Signature:

PPD

Date (DD Mmm YYYY)

Evidence Generation Operations
MA-EST-M

Signature:

PPD

Date (DD Mmm YYYY)

Oncology and Ophthalmology